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9 PHARMACEUTICALS LLC, AND TAKEDA
   PHARMACEUTICALS AMERICA, INC.
10

11   UNITED STATES DISTRICT COURT
                    NORTHERN DISTRICT OF CALIFORNIA
12   SAN FRANCISCO DIVISION

13

TAKEDA PHARMACEUTICAL CO., LTD., TAKEDA PHARMACEUTICALS NORTH AMERICA, INC., TAKEDA PHARMACEUTICALS LLC, AND TAKEDA PHARMACEUTICALS AMERICA, INC., Plaintiffs, v. HANDA PHARMACEUTICALS, LLC, Defendant.	Case No. 3:11-cv-00840 JCS **DECLARATION OF ALLAN S. MYERSON, PH.D., IN SUPPORT OF TAKEDA'S OPENING CLAIM CONSTRUCTION BRIEF** Date: February 16, 2012 Time: 9:30 a.m. Judge: Hon. Joseph C. Spero Courtroom G, 15th Floor
TAKEDA PHARMACEUTICAL CO., LTD., TAKEDA PHARMACEUTICALS NORTH AMERICA, INC., TAKEDA PHARMACEUTICALS LLC, AND TAKEDA PHARMACEUTICALS AMERICA, INC., Plaintiffs, v. ANCHEN PHARMACEUTICALS, INC., AND TWI PHARMACEUTICALS, INC., Defendants.	Case No. 3:11-cv-01609 JCS

1

2   TAKEDA PHARMACEUTICAL CO., LTD.,   Case No. 3:11-cv-01610 JCS
    TAKEDA PHARMACEUTICALS NORTH
3   AMERICA, INC., TAKEDA
    PHARMACEUTICALS LLC, AND TAKEDA
4   PHARMACEUTICALS AMERICA, INC.,

5   Plaintiffs,

6   v.

7   IMPAX LABORATORIES, INC.,

8   Defendant.

9

10 I, Allan S. Myerson, declare as follows:

11   1.   I am currently Professor of the Practice of Chemical Engineering at the

12 Massachusetts Institute of Technology ("MIT") in Cambridge, Massachusetts. I submit this

13 declaration in support of the opening claim construction brief submitted by Plaintiffs Takeda

14 Pharmaceutical Company Limited, Takeda Pharmaceuticals North America, Inc., Takeda

15 Pharmaceuticals LLC, and Takeda Pharmaceuticals America, Inc. (collectively, "Takeda"). In

16 particular, I submit this declaration (a) to provide relevant background information regarding the

17 technology at issue in U.S. Patent Nos. 6,462,058 (the "'058 patent"), 6,664,276 (the "'276

18 patent"), 6,939,971 (the "'971 patent"), and 7,285,668 (the '668 patent") (collectively, the

19 "crystal-form patents"), and U.S. Patent No. 7,737,282 (the "'282 patent") (the "amorphous-form

20 patent"),[1] and (b) to set forth my opinions about the meanings of certain disputed claim terms in

21 these patents from the perspective of a person of ordinary skill in the pertinent field at the relevant

22 times.

23 **I.   QUALIFICATIONS**

24   2.   The following is a brief summary of my background and qualifications. My

25 background and qualifications are more fully set out in my curriculum vitae, attached as Exhibit

26 6.

27 _____

    [1] Copies of the crystal-form patents are attached as Exhibits 1, 2, 3, and 4 respectively. A copy of
28 the amorphous-form patent is attached as Exhibit 5.

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1   3.   I am a chemical engineer by training. I have a particular interest in industrial

2   crystallization and have conducted research in this area for over 30 years.

3   4.   I began my training at Columbia University in New York, where I obtained my

4   Bachelor of Science in chemical engineering in May 1973. Thereafter, I obtained Masters and

5   Ph.D. degrees in chemical engineering from the University of Virginia in January 1975 and

6   January 1977, respectively. I am a registered Professional Engineer in New York and Ohio.

7   5.   In January 1977, I began my academic career as an Assistant Professor of

8   Chemical Engineering at the University of Dayton, where I worked until August 1979.

9   6.   From September 1979 to December 1984, I was a faculty member at the Georgia

10   Institute of Technology in Atlanta, serving first as an Assistant Professor of Chemical

11   Engineering and subsequently as an Associate Professor.

12   7.   In January 1985, I joined the faculty of the Polytechnic University in Brooklyn,

13   New York. While there, I served in various positions including as Joseph and Violet J. Jacobs

14   Professor of Chemical Engineering, Head of the Department of Chemical Engineering, Dean of

15   the School of Chemical and Materials Science and as Vice Provost for Research and Graduate

16   Studies.

17   8.   In January 2000, I moved to the Illinois Institute of Technology in Chicago

18   ("IIT"). I began as Professor of Chemical Engineering and Dean of the Armour College of

19   Engineering and Science. I remained in that position until January 2003, when I became the

20   Philip Danforth Armour Professor of Engineering. Between 2003 and 2008, I was also Provost

21   and Senior Vice President at IIT. I moved from IIT to my current position at MIT in August

22   2010.

23   9.   My current research focuses on crystallization from solution with an emphasis on

24   nucleation, pre-nucleation solution structure, polymorphism, impurity-crystal interactions and

25   industrial applications of crystallization.

26   10.   Over the course of my career, I have supervised the Ph.D. dissertations of

27   approximately 34 students and have supervised the research of approximately 15 post-doctoral

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1   research associates. I currently supervise a research group consisting of four Ph.D. students and

2   four post-doctoral research associates.

3   11.   I have presented the results of my research, including in the area of crystallization,

4   at numerous national and international meetings. I have also published approximately 164 papers

5   in refereed scientific journals. Many of those papers pertain to crystallization and related

6   subjects.

7   12.   I have taught short courses in crystallization (sponsored by the Center of

8   Professional Advancement and the American Chemical Society) in the U.S. and Europe and have

9   taught special crystallization courses at pharmaceutical and chemical companies in the U.S.,

10   Europe, and Japan. I have also consulted for major chemical and pharmaceutical companies in

11   those same regions.

12   13.   In addition to teaching and research, I have edited five books in the area of

13   crystallization, including the *Handbook of Industrial Crystallization: Second Edition* (2001). I

14   am also the Associate Editor of *Crystal Growth and Design*, a journal published by the American

15   Chemical Society. My research accomplishments in the area of crystallization science and

16   technology were recognized by the American Chemical Society that awarded me the 2008 ACS

17   award in Separation Science and Technology.

18   **II.**   **AREA OF EXPERTISE**

19   14.   Based on my experience and qualifications, I consider myself to be an expert in the

20   field of crystallization, polymorphism, nucleation, and their application to the pharmaceutical

21   industry.

22   **III.**   **PRIOR EXPERT TESTIMONY**

23   15.   Within the past five years, I have testified I have testified in the following cases

24   (by deposition or at trial) on behalf of the underlined parties:

25   **1.**   **U.S. Cases: Trial and Deposition Testimony**

26   *Aventis Pharma SA, Sanofi Aventis US,. LLC v. Hospira, Inc,*
      Apotex Corp. (D. Del)

27

28   *Sears Petroleum and Transport Company v. Archer Daniels*
      Midland (N.D.N.Y.)

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1   *Pfizer Inc.* v. *Alphapharm Pty. Ltd.* (D. Del.)

2   **2.   U.S. Cases: Deposition Testimony Only**

3   *Abbott Laboratories* v. *Lupin Limited* (E.D. Va.)

4   *Abbott Laboratories* v. *Teva* (N.D. Ill.)

5   *Wrigley* v. *Cadbury Scheppes* (N.D. Ill.)

6   *Ortho-McNeil Pharm et. al.* v. *Lupin* (D.N.J.)

7   *Shire Canada Inc. et al* v. *Barr Laboratories, Inc.* (S.D.N.Y.)

8   *Pfizer v.* *Dr. Reddy's Laboratory Ltd.* (D. Del.)

9   *Pfizer v.* *Teva* (D. Del.)

10   *Pfizer* v. *Dr. Reddy's Laboratories Ltd.* (D. Del.)

11   *Federal Trade Commission* v. *Cephalon* (D.D.C.)

12   **3.   Canadian Cases: Trial and Deposition Testimony:**

13   *Ortho-McNeil Pharm. et al.* v. *Novopharm*

14   **4.   Canadian Cases: Deposition Testimony Only**

15   *Pfizer* v. *Ratiopharm*

16   *Pfizer* v. *Ranbaxy*

17   *Lilly* v. *Pharmascience*

18   *Pfizer* v. *Apotex*

19   *Pfizer* v. *Pharmascience*

20   *Astra Zeneca* v. *Apotex*

21   *Bristol-Myers Squibb Canada and Merck, Sharpe and Dohme
22   Corp.* v. *Mylan Pharmaceuticals*

23   **IV.   COMPENSATION**

24   16.   I am being compensated for my time at my usual rate of $700 per hour. My

25   compensation is not contingent upon the outcome of the litigation.

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V.   MATERIALS CONSIDERED

2   17.   In addition to the crystal-form and amorphous-form patents, I have considered the

3   materials listed in Exhibit 7. I reserve the right to supplement this declaration based on additional

4   information that is made available to me between now and the time of the *Markman* hearing.

5

VI.   EXECUTIVE SUMMARY

6   18.   I will begin the substantive portion of my declaration by providing background

7   information on the science and technology at issue in this case. I will then briefly set forth the

8   standards that I understand to govern the Court's task of construing disputed patent claim terms. I

9   will then render my opinions on the meaning of three disputed claim terms as those terms are

10 used in the crystal-form and amorphous-form patents.

11   19.   Based on my review of the materials described in paragraph 17, as well as my

12 expertise in crystallization, polymorphism, and analytical techniques related to these subjects, my

13 principal conclusions are as follows:

14   20.   To summarize, my opinions are as follows:

15   A.   The terms "a crystal of" and "a crystalline compound of," as those terms

16 are used in the crystal-form patents, mean "a regularly repeating pattern of molecules with long

17 range order extending in three dimensions."

18   B.   The term "characteristic peaks at interplanar spacings (d)," as that term is

19 used in the '058 and '971 patents, means "a series of peaks that are characteristic of a particular

20 crystal form within normal experimental error of X-ray powder diffraction."

21   C.   The term "melting start temperature," as that term is used in the '668

22 patent, is not indefinite, as one skilled in the art could discern the boundaries of the claim based

23 on the claim language, the specification, and his own knowledge. In my opinion, the phrase

24 "melting start temperature" means "the temperature at which crystals start to melt, represented by

25 the onset temperature of melting as measured by differential scanning calorimetry."

26   D.   A person of ordinary skill in the art of the crystal-form patents would

27 understand the plain and ordinary meaning of the claim term "about," as that term is used in

28 claims 9 and 10 of the '668 patent, to mean "approximately."

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E.   The term "amorphous compound," as that term is used in the '282 patent, means "a non-crystalline solid that lacks the long-range order characteristic of a crystal."

VII.   SCIENTIFIC AND TECHNOLOGICAL BACKGROUND

A.   Crystals

21.   Crystals are solids in which the atoms (or molecules) are arranged in a periodic repeating pattern that extends in three dimensions. When crystals are grown slowly and carefully they are normally bounded by plane faces (flat surfaces extending in different directions) that can be seen with the naked eye. Looking at a common material such as table salt under a magnifying glass will reveal these plane faces. They can also be seen in the beautiful mineral samples that are often displayed in museums.

22.   Not all crystalline materials display these obvious plane faces. Materials such as steel, concrete, bone and teeth are made up of small crystals that can be seen under a light or electron microscope. Still other materials, such as wood, silk, hair, and many solid polymers (plastics) are only partially crystalline or have crystalline regions.

23.   Solids that are not crystalline and have no long range order (meaning that their constituent molecules are similarly oriented for no more than a few molecules) —for instance, glass—are said to be amorphous. Amorphous solids are often (but not always) less chemically stable than crystalline solids. There are a number of reasons why an amorphous solid, rather than a crystalline solid, may form. One common reason is the presence of impurities that block the formation of the crystalline lattice (a term I explain below).

24.   Crystals are made up of molecules that interact with each other to form chemical bonds of different kinds. Chemical bonds are usually classified as ionic, covalent, metallic, van der Waals or hydrogen bonds, with the first three types being stronger than the last two. Organic molecules (that is, molecules containing carbon) form crystals which are known as molecular crystals in which the molecules are held together by weak attractive van der Waals forces.

25.   The internal structure (called the crystal structure or crystalline lattice) of molecular crystals is determined by the position of the molecules relative to each other and

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1   extending in three dimensions, along with the packing arrangement and symmetry elements of the

2   structure.

3   26.   Knowing the internal structure of a crystal allows one to construct a three-

4   dimensional model with all atoms and molecules in the correct location relative to each other. If

5   one thinks of crystals in a geometric sense, a concept known as a point lattice can be used to

6   represent the crystal. A point lattice is a set of points arranged so that each point has identical

7   surroundings. In addition, a point lattice can be characterized in terms of three spatial dimensions

8   — a, b, and c — and three angles — alpha, beta, and gamma. These lengths and angles are

9   known as lattice parameters and a single cell constructed using these parameters is called the unit

10   cell. The dimensions of the unit cell of a crystal (making up a crystal's internal architecture) are

11   unique and can be used to distinguish one crystalline form of a molecule from another.

12   27.   The process by which crystals are formed is called crystallization. Various

13   methods of crystallization exist, the most common being the dissolution of the solid substance in

14   a solution, followed by a step that causes it to precipitate out of the solution by cooling,

15   evaporation, addition of a co-solvent, or some other means.

16   **B.**   **X-Ray Powder Diffraction Analysis**

17   28.   X-ray diffraction is a technique used to identify crystals and to determine crystal

18   structure. Crystal structure can be determined using single crystal x-ray diffraction. In this

19   method a single crystal with dimensions of 0.1 mm in all dimensions must be prepared. This

20   crystal is then mounted on a goniometer and rotated while being exposed to x-rays. The resulting

21   data can then be analyzed to determine lattice type, unit cell dimensions and the location of each

22   atom in the crystal relative to the other atoms, thus enabling a three dimensional understanding of

23   the crystal structure.

24   29.   Another type of x-ray diffraction known as powder x-ray diffraction (also called x-

25   ray powder diffraction, or XRPD) is also used to identify crystals. In XRPD, samples are also

26   mounted on a goniometer and exposed to x-rays. In the case of XRPD, a small amount of ground

27   crystalline powder, rather than a single crystal, is analyzed. XRPD produces a pattern of peaks

28   that acts as a signature or fingerprint for that substance.

1   30.   XRPD involves the use of a sample of the material of interest that has been ground

2 into a fine powder. When x-rays of wavelengths of 0.5-2.5 Angstroms are directed at a

3 crystalline solid, an observable pattern is produced because the distances between atoms in a

4 crystal are of a length similar to the x-ray wavelength. When the x-ray wavelength equals (or is

5 an integer of) the distance between adjacent crystal planes, x-rays encountering adjacent crystal

6 planes will diffract or scatter off the crystals in phase with one another, resulting in constructive

7 interference and an intensifying of the amplitude of the reflected x-ray. The relationship between

8 the wavelength of the x-rays and the spacing between atoms in a crystal is known as Bragg's law:

9 $$n\lambda = 2d \sin\theta$$

10 where λ is the wavelength of the incident x-rays, d is the interplanar spacing in the crystal and θ is

11 the angle of incident x-rays on the crystal.

12   31.   XRPD relies on the fact that the array of tiny crystals in the powder sample,

13 randomly arranged, will present all possible lattice planes for reflection of an incident beam of x-

14 rays. In XRPD, a device (called a diffractometer) plots the intensity of the diffracted x-rays at

15 various angles of the incident x-rays ("Bragg angles"). XRPD data is often reported in terms of

16 d-spacings and Bragg angles (known as 2θ or "two theta" values) as well as relative intensities

17 (all peaks are divided by the intensity of the maximum peak). The two theta values are a function

18 of the wavelength of the x-rays used.   In other words, the angle of incidence (and diffraction)

19 necessary for constructive interference to occur will vary based upon the wavelength of the x-ray.

20 The d-spacings as a property of the crystalline solid, on the other hand, are invariant. When x-ray

21 data is reported in terms of two theta angles, the wavelength, or the x-ray source, is also provided.

22 Data taken at different wavelengths can always be compared by conversion to d-spacings. D-

23 spacing data can always be used to calculate two-theta angles for any x-ray wavelength.

24   32.   The x-ray pattern (particularly the location of the peaks) acts as a 'fingerprint' for

25 a given crystal form of a particular compound and a selection of peaks from an XRPD pattern can

26 be used to identify a compound and its crystalline phase. When XRPD analysis is performed, the

27 number of detected peaks and their intensities depend on the size of the sample, the scanning

28 speed used in the diffractometer, the degree to which the sample was ground, and the crystallinity

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1   of the sample. Because of these variations, substances are normally characterized by a number of

2   the major or most intense peaks.

3   33.   In the pharmaceutical industry, XRPD is the most commonly used method of x-ray

4   analysis for identifying crystals.

5   **C.   Nature of Polymorphs**

6   34.   The crystal structure of a material determined by XRPD gives a picture of the

7   arrangement of the atoms (or molecules) of the chemical species in the crystalline state. It is

8   possible, however, for a given chemical species to have the ability to crystallize into more than

9   one distinct crystal structure. This ability is called polymorphism (allotropism if the species is an

10   element such as carbon).

11   35.   Different polymorphs of the same material can display significantly different

12   properties as well as structures. A dramatic example is carbon, which can crystallize as graphite

13   or as diamond. Properties such as hardness, density, electrical conductivity and shape are very

14   different for these two solids. These significant differences in properties, brought about by

15   differences in crystal structure, are not unique to carbon; they can occur in all materials that

16   display polymorphism. Other properties that normally vary in polymorphs of a given substance

17   include solubility, dissolution rate, and vapor pressure, among others. Polymorphism is quite

18   common in inorganic and organic species. Organic molecular crystals often have multiple

19   polymorphs that can be of great significance in the pharmaceutical, dye, and explosives

20   industries.

21   36.   At a given temperature, one polymorph is the thermodynamically stable form.

22   This does not mean that other polymorphs cannot exist under those conditions; it means only that

23   one polymorph is stable and any others present can convert to the stable polymorphic form. The

24   rate of this transition, or whether it occurs at all, is dependent on various conditions, such as

25   temperature, pressure, presence of solvent, etc.

26   37.   Pseudo-polymorphism refers to the ability of certain chemical species to

27   crystallize in a structure that contains a solvent as part of the crystal lattice (that is, as the crystal

28   forms, some molecules of the solvent are trapped inside the lattice). These crystals are also

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known as solvates. A solvate in which the solvent is water is usually referred to as a hydrate. For a given pseudo-polymorph, the ratio of the number of molecules of solvent to the number of molecules of the chemical species itself is fixed.

38.   Just as a crystal form of an active pharmaceutical ingredient may have different properties as compared to an amorphous form, different polymorphs or hydrates of a pharmaceutical compound may have significantly different chemical and physical characteristics from one another, which may affect the manufacturability, performance, and/or quality of the drug product.

D.   Enantiomers

39.   Enantiomers are pairs of compounds that contain chemical formulas and atomic sequences identical to one another, but which differ in their orientation in three-dimensional space. The physical orientation of enantiomers is such that they constitute non-superimposable mirror images of one another, in the way that a person's left hand is a non-superimposable mirror image of their right hand. Enantiomers, which are also known as chiral molecules, are designated as right (R+) and left (S-), or (+) and (-).[2]   In nature, compounds having enantiomeric properties exist as racemic mixtures, meaning that they contain equal amounts of the right- and left-enantiomer.

40.   Chiral molecules are important in the pharmaceutical industries because in some cases the biological activity of the enantiomers can have significant differences. When compounds which have enantiomeric properties are synthesized, the result is often a mixture of the enantiomers which is known as a racemic mixture.
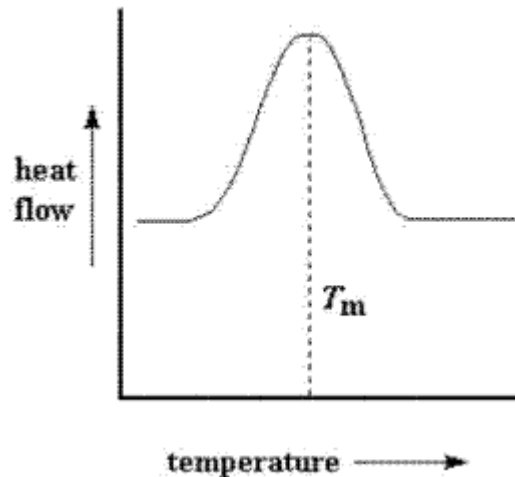
E.   Differential Scanning Calorimetry

41.   Differential Scanning Calorimetry (DSC) is an analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and a reference is measured as a function of temperature.

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[2] Enantiomers rotate plane-polarized light in opposite directions, and the designations above refer to that direction of rotation.

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1   42.   The DSC device contains two pans: a sample pan and a reference pan. The

2 reference pan is left empty. Each pan sits on top of a heater controlled by a computer. When the

3 experiment starts, the computer turns on the heaters to heat the pans at a specific rate, such as

4 5° C per minute. The computer makes sure that the two separate pans, with their two separate

5 heaters, heat at the same rate as each other. The presence of the sample causes the heater

6 underneath the sample pan to work harder than the heater underneath the reference pan to reach

7 an equivalent temperature. The DSC measures the difference in the amount of extra heat required

8 to heat the sample.

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19 **FIGURE 1** (from Ex. 8 at DEX0014728 ("Differential Scanning Calorimetry," The University of Southern Mississippi Polymer Science Learning Center, *at http://www.pslc.ws/mactest/dsc.htm* (DEX0014724-730)).

20

21   43.   When a crystal melts, that event is reflected by a peak in the DSC curve. This is

22 because energy in the form of heat is required to melt a material. This energy of melting is

23 reflected in a peak in the DSC curve where the sample is requiring more energy that the reference

24 to maintain and increase the temperature. An example is shown in Figure 1 above.

25 **F.   The Patents-in-Suit**

26   44.   The patents-in-suit relate to dexlansoprazole, an enantiomer of lansoprazole.

27 Lansoprazole is a racemic mixture of the enantiomers dexlansoprazole (the right, R+, or (+)

28 enantiomer) and levolansoprazole (the left, S-, or (-) enantiomer). Takeda manufactures and sells

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1   Dexilant, a delayed-release dexlansoprazole formulation for treating acid reflux disease and

2   erosive esophagitis. Dexilant is the commercial embodiment of several of the patents in suit.

3   45.   The patents-in-suit relate to compositions of, or methods of treatment using,

4   dexlansoprazole, a drug used to treat erosive esophagitis and non-erosive gastroesophageal reflux

5   disease.

6   46.   The '058, '276, '971, and '282 patents are part of the same patent family and have

7   the same inventors, Akira Fujishima, Isao Aoki, and Keiji Kamiyama. These four patents claim

8   priority to a Japanese patent application filed June 17, 1999. The asserted claims in the '058,

9   '276, and '971 patents all relate to crystal forms of dexlansoprazole, or methods of treating

10 medical conditions using such crystal forms.

11   47.   More specifically, the '058 patent claims two specific types of crystal forms of

12 dexlansoprazole characterized by distinctive XRPD patterns. One crystal is the anhydrous (non-

13 water-containing) crystal, while the other is a sesquihydrate. The dexlansoprazole sesquihydrate

14 is a crystalline compound in which 1.5 molecules of water are incorporated into the crystal lattice

15 for each molecule of dexlansoprazole.

16   48.   The '276 patent claims any crystalline compound of dexlansoprazole. The '971

17 patent, *inter alia*, claims methods of treating reflux esophagitis using an effective amount of a

18 dexlansoprazole crystalline compound, and includes claims applicable both to the particular

19 crystal forms claimed in the '058 patent, and applying to any crystalline form. The asserted

20 claims of the '282 patent relate to an amorphous (i.e., non-crystalline) compound of

21 dexlansoprazole and a pharmaceutical composition comprised of amorphous dexlansoprazole.

22   49.   The asserted claims of the '668 patent relate to particular subsets of crystal forms

23 of dexlansoprazole characterized by particular melting start temperatures. The '668 patent claims

24 priority to a Japanese patent application filed December 1, 2000. *See id.*, Title Page (30) (foreign

25 application priority data).

26 **VIII.   PERSON OF ORDINARY SKILL IN THE ART**

27   50.   In my opinion, the level of skill in the art of the invention of the Crystal-Form and

28 Amorphous-form patents is a bachelor's degree in chemistry, chemical engineering, or related

1   disciplines, with a minimum of three years experience in the pharmaceutical industry related to

2   organic synthesis, API (active pharmaceutical ingredient) manufacturing, crystallization or

3   detection and/or evaluation of solid state forms, or an advanced degree in chemistry, chemical

4   engineering, or related disciplines, with less or no experience.

5   **IX.   CLAIM CONSTRUCTION**

6   **A.   Legal Standards**

7   51.   I understand that claim terms are to be construed in accordance with their ordinary

8   and customary meaning, with the ordinary and customary meaning referring to how a person of

9   ordinary skill in the art would understand a claim term at the time of the invention. I further

10   understand that a person of ordinary skill is deemed to read the claim term in the context of the

11   entire patent, including the other claims and the written description, and that the written

12   description in particular plays a "key role" in the interpretation of the claims.

13   52.   I further understand that, unless a patentee defines a term differently in the patent

14   specification either expressly or by clear implication, a claim term generally should be afforded

15   its ordinary and customary meaning as it would be understood by a person of ordinary skill in the

16   art, taking into account the language of the claims themselves and the teachings of the

17   specification.

18   53.   Additionally, I understand that the prosecution history may reflect whether the

19   inventor limited the invention in the course of prosecution, and that a clear and deliberate

20   statement evidencing a disclaimer of claim scope may support a narrowing of the claim scope

21   beyond what the claims and specification would otherwise suggest.

22   54.   The opinions set forth below are intended to address those issues relevant to claim

23   construction that fall within my area of expertise — i.e., Crystallization, polymorphism, and

24   analytical methods such as XRPD and DSC associated with the analysis and testing of crystalline

25   materials.

26   **B.   "A Crystal Of" and "A Crystalline Compound Of"**

27   55.   The term "a crystal of" appears in claims 1-4 of the '058 patent and claims 9 and

28   10 of the '668 patent, and the term "a crystalline compound of" appears in and claims 2 and 3 of

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the '276 patent and claims 6, 7, 8 of the '971 patent. The usage of the term "a crystal of" in claim

1 of the '058 patent is typical:

> **A crystal of** (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1 H-benzimidazole wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

(Emphasis added.)

56.   It is my opinion, based on my experience and the evidence I have considered, that

a person of ordinary skill in the art, reading the crystal-form patents in 1999, would have

understood the disputed term "a crystal of" and "a crystalline compound of" to be "a regularly

repeating pattern of molecules with long range order extending in three dimensions." I

understand that Handa and Impax agree with this construction, while TWi/Anchen has stated that

these terms require no construction.

57.   Takeda, Handa, and Impax's proposed construction of a crystal as "a regularly

repeating pattern of molecules with long range order extending in three dimensions" was

generally accepted in the field in 1999, and it has not changed since that time. This understanding

is reflected in the following literature references that are accepted authorities in the field of

crystallography:

Exhibit	Reference	Relevant Definition
9	C.W. Bunn, *Chemical Crystallography* (2d ed. 1961) (DEX0014499-502), at DEX0014501.	"crystalline" means that "the atoms or molecules of which [a solid substance is] composed are packed together in a regular manner, forming a three-dimensional pattern"
10	Bruno C. Hancock and George Zografi, *Characteristics and Significance of the Amorphous State in Pharmaceutical Systems*, 86 J. Pharm. Sci. 1-12 (1986) (DEX0014581-592), at DEX0014581.	"crystalline material" normally possesses "three-dimensional long-range order"
11	S.R. Elliott, *Physics of Amorphous Materials* 1-6 (2d ed. 1990) (DEX0014509-555), at DEX0014512.	"A perfect crystal in which the atoms (or groups of atoms or 'motifs') are arranged in a pattern that repeats periodically in three dimensions to an infinite extent."

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Exhibit	Reference	Relevant Definition
12	Allan S. Myerson & Rajiv Ginde, *Crystals, Crystal Growth, and Nucleation, in Handbook of Industrial Crystallization* 33-65 (2d ed. 2002) (DEX0014612-44), at DEX0014612.	"Crystals are solids in which the atoms are arranged in a periodic repeating pattern that extends in three dimensions."
13	Richard Zallen, *The Physics of Amorphous Solids* 1-5 (2004) (DEX0014766-799), at DEX0014770.	In crystals, "[t]he atomic positions exhibit long-range order."
14	Hsien-Hsin Tung et al., *Crystallization of Organic Compounds: An Industrial Perspective* 25-29 (2009) (DEX0014717-723), at DEX0014719.	"Crystalline materials are solids in which molecules are arranged in a periodical three-dimensional pattern."

58.   The definition for a crystal set forth in the extrinsic evidence proffered by

TWi/Anchen also supports Takeda's proposed construction of "a regularly repeating pattern of

molecules with long range order extending in three dimensions." The *McGraw-Hill Concise*

Encyclopedia of Science and Technology, (Sybil P. Parker ed., 3d ed. 1994) (IPXL-0009905–13),

defines a "crystal" as "a solid throughout which the atoms and molecules are arranged in a

regularly repeating pattern." Ex. 15 at 510 (IPXL-0009909).

59.   Accordingly, the person of ordinary skill would understand the claim terms "a

crystal of" and "a crystalline compound of" to refer to "a regularly repeating pattern of molecules

with long range order extending in three dimensions."

C.   "Characteristic Peaks at Interplanar Spacings (d)"

60.   The term "characteristic peaks at interplanar spacings (d)" appears in claims 1 and

2 of the '058 patent and claim 7 of the '971 patent. The usage of the term "characteristic peaks at

interplanar spacings (d)" in claim 1 of the '058 patent exemplifies how this term is used in the

claims:

> A crystal of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1 H-benzimidazole wherein the X-ray powder diffraction analysis pattern has **characteristic peaks at interplanar spacings (d)** of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

(Emphasis added.)

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61.   It is my opinion, based on my experience and the evidence I have considered, that a person of ordinary skill in the art, reading the '058 and '971 patent in 1999, would have understood the disputed term "characteristic peaks at interplanar spacings (d)" to mean "a series of peaks that are characteristic of a particular crystal form within normal experimental error of X-ray powder diffraction."

62.   I am informed that Defendants have proposed to construe "characteristic peaks of interplanar spacings (d)" to mean "peaks in the X-ray powder diffractogram of a crystal that uniquely identify that crystal, denoted by distances between lattice planes in a crystal as measured by a diffraction experiment and defined by Bragg's law." Like Takeda's proposed construction, Defendants' construction acknowledges that "characteristic peaks of interplanar spacings (d)," known as d-spacings for short, are measured using x-ray diffraction analysis, and that a series of peaks acts as a signature or fingerprint for a particular substance. Defendants' construction goes on to state that the interplanar spacings (d) represent the "lattice planes in a crystal as measured by a diffraction experiment and defined by Bragg's law," by which Defendants appear to be referring to the fact that the values given for the interplanar spacings (d) can be calculated using Bragg's law ($n\lambda = 2d \sin \theta$) by measuring the angle (θ) at which the x-ray beam (at wavelength λ) is scattered or diffracted as it bounces off of the lattice planes of a crystal. I do not disagree with this description of how XRPD diffraction measurements are conducted, although I do not believe that this level of detail is necessary to provide a clear meaning to the claim limitation.

63.   My major disagreement with Defendants' construction is that it does not incorporate the notion of experimental error. A person of ordinary skill in 1999 would have understood any description of "characteristic peaks of interplanar spacings (d)" to be within the context of the normal experimental error inherent to XRPD measurements because of limitations in the measuring equipment or techniques.

64.   In fact, the United States Pharmacopeia ("USP"), which is the official pharmacopeia of the United States,[3] addresses the reproducibility of XRPD measurements. The

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[3] Prescription and over-the-counter medicines and other health care products sold in the United States are required to follow the standards in the United States Pharmacopeia–National Formulary.

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1   1995 edition of the USP states that "[a]greement between sample and reference should be within

2   the calibrated precision of the diffractometer for diffraction angle (2 values should typically be

3   reproducible to ±0.10 or 0.20 degrees), while relative intensities between sample and reference

4   may vary up to 20 percent." Ex. 16 at DEX0014738 ("X-Ray Diffraction," *The United States*

5   *Pharmacopeia*, 1843-44 (23d rev. 1995) (DEX0014735–38)). The 2002 edition of the USP

6   provides for the same ±0.10 or 0.20 degree range for experimental error.[4] Ex. 17 at

7   DEX0014742 ("X-Ray Diffraction," *The United States Pharmacopeia*, 2088-89 (25th rev. 2002)

8   (DEX0014739–42)). The 2005 edition of the USP, reflecting improvements in XRPD

9   technology, narrowed the error range to ±0.10 degrees. Ex. 18 at DEX0014746 ("X-Ray

10   Diffraction*," The United States Pharmacopeia*, 2513-14 (28th rev. 2005) (DEX0014743–46)).

11   65.   Thus, in June 1999, when the Japanese patent applications leading to the '058 and

12   '971 patents were filed, there was an acknowledged imprecision in XRPD diffraction angles of

13   ±0.10 to ±0.20 degrees. It follows from Bragg's law that an error in the diffraction angles is

14   related to an error in d-spacing. Therefore, experimental error in the measurements of diffraction

15   angles translates into error in the calculation of d-spacings. One of ordinary skill in the art would

16   be able to calculate readily for any given wavelength the range in d-spacings equivalent to the

17   angles including the error.

18   66.   The experimental error inherent in XRPD measurements has been recognized by

19   other accepted authorities in the field of crystallography. For example, in the article by Sisir

20   Bhattacharya, Harry G. Brittain, and Raj Suryanarayanan, *Thermoanalytical and*

21   *Crystallographic Methods*, *in Polymorphism in Pharmaceutical Solids*, 318-46 (2d ed. 2009)

22   (DEX0014472–88), the authors cite to the USP for the range of experimental error permitted in

23   XRPD measurements:

24   The United States Pharmacopeia contains a general chapter on
                    XRD, which sets the criterion that identity is established if the
25   scattering angles in the powder patterns of the sample and reference

26   ───────────────────────
     [4] The 2002 edition of the USP also abolished the 20% tolerance standard for relative intensities
27   between sample and reference, noting that these intensities might vary "considerably." *See* Ex. 17
     at DEX0014742 ("X-Ray Diffraction," *The United States Pharmacopeia*, 2088-89 (24th rev.
28   2002) (DEX0014739–42)).

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> standard agree to within the calibrated precision of the diffractometer. It is noted that it is generally sufficient that the scattering angles of the ten strongest reflections obtained for an analyte agree to within either ±0.10 or 0.20° 2θ, whichever is more appropriate for the diffractometer used. Older versions of the general test contained an additional criterion for relative intensitives of the scattering peaks, but it has been noted that relative intensities may vary considerably from that of the reference standard, making it impossible to enforce a criterion based on the relative intensities of corresponding scattering peaks.

Ex. 19 at 333-34 (DEX0014481-82). Another article by Brittain in an earlier of edition of *Polymorphism in Pharmaceutical Solids*, cited by Defendants in support of their proposed construction, also acknowledges that the "USP general chapter on x-ray diffraction states that identity is established if the scattering angles of the ten strongest reflections obtained for an analyte agree to within ±0.20 degrees with that of the reference material, and if the relative intensities of these reflections do not vary by more than 20 percent." Ex. 20 at IPXL-0009873 (Harry G. Brittain, "Methods for the Characterization of Polymorphs and Solvates," *in Polymorphism in Pharmaceutical Solids*, 227 (1st ed. 1999) (IPXL-0009869–9875)).

67.   Because one skilled in the art would understand that XRPD measurements are inherently imprecise, it is my opinion that the claim term "characteristic peaks at interplanar spacings (d)" should be construed to include the notion of normal experimental error, as provided for in Takeda's proposed construction.

D.   "Melting Start Temperature"

68.   The term "melting start temperature" appears in claims 9 and 10 of the '668 patent. As relevant here, Claim 9 claims a crystal of dexlansoprazole "having a melting start temperature of not lower than about 131° C." Claim 10, which depends from claim 9, claims a crystal "wherein the melting start temperature is about 135° C."

69.   It is my opinion, based on my experience and the evidence I have considered, that a person of ordinary skill would be able to discern a meaning for the term "melting start temperature" in the '668 patent, which term Defendants have contended is indefinite, and that the meaning of the term is "the temperature at which crystals start to melt, represented by the onset temperature of melting as measured by differential scanning calorimetry."

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1   70.   The '668 patent claims dexlansoprazole crystals different from, and developed

2   later than, those claimed in the '058, '276, and '971 patents. The '668 inventors used the

3   relatively high "melting start temperature" of the novel crystal form of dexlansoprazole disclosed

4   in the '668 patent to distinguish it from the dexlansoprazole crystal forms disclosed in the earlier

5   patents:

6   > The crystal has the melting start temperature of not less than about
    > 131° C., preferably about 131° C. to about 137° C., more preferably
7   > about 132° C. to about 135° C., most preferably about 133° C. to
    > about 135° C., particularly preferably about 135° C. . . .
8

9   > The melting start temperature of the crystal obtained by a
    > conventional method is less than about 131° C. . . .

10 > The crystal having a melting start temperature of not less
    > than about 131° C. . . . obtained by the production method of the
11 > present invention[] has extremely superior preservation stability as
    > compared to the crystal having a melting start temperature of less
12 > than about 131° C., which is obtained by a prior art method.

13
    '668 patent, col.12, ll.8-27.
14
15 71.   The '668 specification defines the term "melting start temperature" as "the

16 temperature at which crystals start to melt when heated under, for example, the DSC

17 measurement conditions to be mentioned below." '668 patent, col.12, ll.4-7. As discussed in

18 paragraph 41 above, DSC, or differential scanning calorimetry, is a method of measuring phase

19 transitions in a material, such as melting, as a material is heated. The '668 specification also

20 describes the specific DSC conditions under which "melting start temperature" can be measured:

21 > The melting start temperature was measured using DSC
    > (differential scanning calorimeter SEIKO DSC220C) under the
22 > following measurement conditions.

23 > DSC Measurement Conditions;

24 > temperature range: room temperature to 220° C.

25 > temperature rise rate: 0.5° C./min.

26 > sample container: aluminum pan (without cover)

27 > atmosphere: nitrogen gas (100 mL/min)

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2   '668 patent, col.16, ll.15-22. Dr. Tadashi Urai, one of the inventors of the '668 patent, also

3   submitted a declaration to the U.S. Patent and Trademark Office in which he described using

4   DSC to measure the melting start temperatures of three crystals disclosed in the '058 patent. *See*

    Ex. 21 ('668 File History, Decl. of Tadashi Urai, dated Sept. 6, 2005 (DEX0003568-70)).

5   72.   Takeda's proposed construction, "the temperature at which crystals start to melt,

6   represented by the onset temperature of melting as measured by differential scanning

7   calorimetry," thus tracks the definition and description of "melting start temperature" in the

8   specification as well as the disclosure of DSC as the measurement equipment.

9   73.   Moreover, the term "melting start temperature" is well-understood by people of

10 ordinary skill in the field to refer to the onset temperature of melting. This definition was

11 generally accepted in the field in 2000, and it has not changed since that time. For example, the

12 1995 edition of the USP states that, for thermal analysis measurements performed by heating a

13 substance in a glass tube, "[t]he temperature at which the column of the substance under test is

14 observed to collapse definitely against the side of the tube at any point is *defined as the beginning*

15 *of melting*." Ex. 22 at DEX0014733 ("Melting Range or Temperature*," The United States*

16 *Pharmacopeia*, 1805-06 (25th rev. 1995) (DEX0014731–34)). Similarly, the 2005 edition of the

17 USP provides that, when a heat phase test is performed using an apparatus having a detector

18 signal to monitor the melting process, the "beginning of melting" is defined as "the temperature at

19 which the detector signal first leaves its initial value." Ex. 23 at DEX0014750 ("Melting Range

20 or Temperature," *The United States Pharmacopeia*, 2433-34, 2434 (28th rev. 2005)

21 (DEX0014747–50)).   The USP thus has consistently defined the "beginning of melting" as the

22 first detectable sign of a phase change.

23   74.   Indeed, the 2005 edition of the USP also notes, a melting "'onset'. . . temperature

24 can be determined objectively and reproducibly, often to within a few tenths of a degree." Ex. 24

25 at DEX0014754 ("Thermal Analysis," *The United States Pharmacopeia*, 2501-03 (28th rev.

26 2005) (DEX0014751–55)).

27

28

1   75.   Accordingly, in my opinion, one of ordinary skill in the relevant field would

2 understand the boundaries of the claim term "melting start temperature" and would construe the

3 term to mean "the temperature at which crystals start to melt, represented by the onset

4 temperature of melting as measured by differential scanning calorimetry," in light of the claim

5 language, the specification, the prosecution history, and the skilled person's knowledge of the

6 relevant art.

7   **E.**   **"About"**

8   76.   The term "about" appears in claims 9 and 10 of the '668 patent. As relevant here,

9 Claim 9 claims a crystal of dexlansoprazole "having a melting start temperature of not lower than

10 *about* 131° C." (Emphasis added.) Claim 10, which depends from claim 9, claims a crystal

11 "wherein the melting start temperature is *about* 135° C." (Emphasis added.)

12   77.   It is my opinion, based on my experience and the evidence I have considered, that

13 a person of ordinary skill in the art of the crystal-form patents would understand the plain and

14 ordinary meaning of the phrase "about" to mean "approximately." *See* Ex. 25 at DEX0014802

15 *(Webster's Third New International Dictionary*, 5 (1966) at "[1]about" (DEX0014800-802))

16 (defining "about" as "approximately").

17   78.   I understand that Defendants' proposed construction of "about" is "with a variation

18 of no more than 0.5° C. Accordingly, 'about 131° C' includes temperatures between 130.5° C

19 and 131.5° C, and 'about 135° C' includes temperatures between 134.5° C and 135.5° C."

20 However, in my opinion, the person or ordinary skill reviewing the '668 patent and its

21 prosecution history would not understand the term "about" to possess the precise meaning of

22 "with a variation of 0.5° C." The '668 specification does not use the term "about" in a manner

23 that would indicate the range of values that it is intended to encompass.   Nor does the

24 prosecution history provide a basis for further specifying the scope of the claim. Accordingly, the

25 person of ordinary skill would construe the term "about" to have its usual meaning of

26 "approximately."

27

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F.   "Amorphous Compound"

79.   The term "amorphous compound" appears in claims 1 and 2 of the '282 patent. Claim 1 claims "[a]n amorphous compound of [dexlansoprazole] or a salt thereof." Claim 2, which depends from claim 1, claims "[a] pharmaceutical composition comprising the amorphous compound according to claim 1 and a pharmaceutically acceptable excipient, carrier or diluent."

80.   It is my opinion, based on my experience and the evidence I have considered, that a person of ordinary skill in the art reading the '282 patent in 1999 would have understood the disputed term "amorphous compound" to mean "a non-crystalline solid that lacks the long-range order characteristic of a crystal."

81.   As I stated above in paragraphs 55-59, the generally accepted definition of a crystal — both in 1999 and presently — is "a regularly repeating pattern of molecules with long range order extending in three dimensions." Solids can be crystalline or amorphous. Unlike a crystal, an amorphous solid lacks long-range three-dimensional order. This understanding is reflected in the following literature references that are accepted authorities in the field:

Exhibit	Reference	Relevant Definition
10	Bruno C. Hancock and George Zografi, *Characteristics and Significance of the Amorphous State in Pharmaceutical Systems*, 86 J. Pharm. Sci. 1-12 (1986) (DEX0014581-592), at DEX0014581.	"The three-dimensional long range order that normally exists in crystalline material does not exist in the amorphous state . . . ."
11	S.R. Elliott, *Physics of Amorphous Materials*, 6 (2d ed. 1990) (DEX0014509-555), at DEX0014516.	"Amorphous materials do not possess the long-range translational order (periodicity) characteristic of a crystal."
26	Theodore L. Brown et al., *Chemistry, The Central Science*, G-1 (8th ed. 2000) (DEX0014492–94), at DEX0014494.	defining "amorphous solid" to mean "a solid whose molecular-arrangement lacks a regular, long-range pattern"
12	Allan S. Myerson and Rajiv Ginde, *Crystals, Crystal Growth, and Nucleation, in Handbook of Industrial Crystallization* 33 (2d ed. 2002) (DEX0014612-644), at DEX0014612.	"Materials that have short-range order rather than long-range ordering, like glass, are non-crystalline solids. A noncrystalline solid is often referred to as an amorphous solid."
13	Richard Zallen, *The Physics of Amorphous Solids* 1-5 (2004) (DEX0014766-99), at DEX0014770.	"In amorphous solids, long-range order is absent; the array of equilibrium atomic positions is strongly disordered."

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Exhibit	Reference	Relevant Definition
27	James E. Brady and Fred Senese, *Chemistry: Matter and Its Changes*, G-1 (4th ed. 2004) (DEX0014489–91), at DEX0014491.	defining "amorphous solid" as "[a] noncrystalline solid"
14	Hsien-Hsin Tung et al., *Crystallization of Organic Compounds: An Industrial Perspective* 25 (2009) (DEX0014717-723), at DEX0014719.	"Amorphous materials are solids in which molecules do not have a periodical three-dimensional pattern."

82.   The person of ordinary skill reading the specification and claims of the '282 patent would understand the term "amorphous compound" to refer to an amorphous solid, for several reasons.

83.   First, the specification provides two examples of what it describes as an "amorphous substance": the product of Reference Example 1 and the product of Reference Example 2. Reference Examples 1 and 2 describe the isolation of optically pure dexlansoprazole from a starting material consisting of racemic lansoprazole (containing both the right and left enantiomers). The specification states that the isolated dexlansoprazole was "evaporated to dryness to yield R(+)-lansoprazole . . . as an amorphous substance." '282 patent, col.8, ll.3-6; '282 col.8, ll.25-29. This reference to drying the amorphous substance indicates that the amorphous substance was in a solid form.

84.   In addition, Experimental Example 2 goes on to compare the stability of the amorphous form of dexlansoprazole to the crystal form:

> The crystals of R(+)-lansoprazole as obtained in Example 2 (about 5 mg) and amorphous R(+)-lansoprazole as obtained in Reference Example 1 (about 5 mg) were each taken in a colorless glass bottle, and their stability during storage at 60° C. (stopper removed) was examined. A 25 ml solution (concentration: about 0.2 mg/ml) of the sample after completion of storage in the mobile phase, along with a standard solution prepared using the initial lot, was analyzed under the HPLC conditions shown below, and the R(+)-lansoprazole content (residual percentage) was calculated from the peak area obtained. . . .
>
> When the sample was stored at 60° C. (exposed), the crystal of Example 2 retained a content exceeding 90% for up to 4 weeks, whereas the amorphous form of Reference Example 1 showed reduction in content to 70.8% after 1 week and 57.5% after 2 weeks. This finding demonstrates that the crystal of R(+)-

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               lansoprazole is more stable and more preferable for use as a
pharmaceutical etc. than the amorphous form.

3   *Id.*, col.14, ll.4-14, 41-47. Crystals are solid substances. One skilled in the art would understand

4   that a stability test comparing an amorphous compound to a crystalline compound would involve

5   a comparison of like to like, namely two solid compounds. Thus, a person of ordinary skill

6   reviewing the patent would understand the inventors' choice of the terms "amorphous compound"

7   and "amorphous substance" instead of "liquid" or "oil" signifies that the amorphous substance

8   referred to is a solid.

9   85.   Because the specification contrasts the "amorphous" dexlansoprazole substance

10   with the "crystal" compound, it is my opinion that the person of ordinary skill would construe the

11   term "amorphous compound" to mean "a non-crystalline solid that lacks the long-range order

12   characteristic of a crystal."

13   **X.   CONCLUSIONS**

14   86.   To summarize, my opinions are as follows:

15   A.   The terms "a crystal of" and "a crystalline compound of," as those terms

16   are used in the crystal-form patents, mean "a regularly repeating pattern of molecules with long

17   range order extending in three dimensions."

18   B.   The term "characteristic peaks at interplanar spacings (d)," as that term is

19   used in the '058 and '971 patents, means "a series of peaks that are characteristic of a particular

20   crystal form within normal experimental error of X-ray powder diffraction."
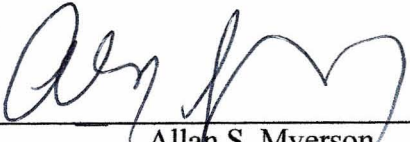
21   C.   The term "melting start temperature," as that term is used in the '668

22   patent, is not indefinite, as one skilled in the art could discern the boundaries of the claim based

23   on the claim language, the specification, and his own knowledge. In my opinion, the phrase

24   "melting start temperature" means "the temperature at which crystals start to melt, represented by

25   the onset temperature of melting as measured by differential scanning calorimetry."

26   D.   A person of ordinary skill in the art of the crystal-form patents would

27   understand the plain and ordinary meaning of the claim term "about," as that term is used in

28   claims 9 and 10 of the '668 patent, to mean "approximately."

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E.   The term "amorphous compound," as that term is used in the '282 patent, means "a non-crystalline solid that lacks the long-range order characteristic of a crystal."

87.   I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Executed on November 4, 2011, at Cambridge MA .

Allan S. Myerson

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